OBSTETRICS

Week-by-week alcohol consumption in early pregnancy and spontaneous abortion risk: a prospective cohort study

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BACKGROUND: Half of women use alcohol in the first weeks of gestation, but most stop once pregnancy is detected. The relationship between timing of alcohol use cessation in early pregnancy and spontaneous abortion risk has not been determined.

OBJECTIVE: This study aimed to evaluate the association between week-by-week alcohol consumption in early pregnancy and spontaneous abortion.

STUDY DESIGN: Participants in *Right from the Start*, a community-based prospective pregnancy cohort, were recruited from 8 metropolitan areas in the United States (2000–2012). In the first trimester, participants provided information about alcohol consumed in the prior 4 months, including whether they altered alcohol use; date of change in use; and frequency, amount, and type of alcohol consumed before and after change. We assessed the association between spontaneous abortion and week of alcohol use, cumulative weeks exposed, number of drinks per week, beverage type, and binge drinking.

RESULTS: Among 5353 participants, 49.7% reported using alcohol during early pregnancy and 12.0% miscarried. Median gestational age at change in alcohol use was 29 days (interquartile range, 15–35 days). Alcohol use during weeks 5 through 10 from last menstrual period was associated with increased spontaneous abortion risk, with risk peaking for use in week 9. Each successive week of alcohol use was associated with an 8% increase in spontaneous abortion relative to those who did not drink (adjusted hazard ratio, 1.08; 95% confidence interval, 1.04–1.12). This risk is cumulative. In addition, risk was not related to number of drinks per week, beverage type, or binge drinking.

CONCLUSION: Each additional week of alcohol exposure during the first trimester increases risk of spontaneous abortion, even at low levels of consumption and when excluding binge drinking.

Key words: alcohol, miscarriage, pregnancy, prospective cohort, spontaneous abortion

Introduction

The line between how alcohol is used before and during pregnancy is blurred in the first weeks of gestation. Although 10% of women continue to use alcohol through pregnancy, as many as half of pregnancies are exposed around conception.[1–5] The tendency to use alcohol until pregnancy detection is consistent among both women with intended and unintended pregnancies, which suggests that preemptive change in alcohol use when planning a pregnancy is not typical.[6] Previous studies on alcohol neglect or cannot capture information about the timing of exposure in early pregnancy, which may obscure or underestimate the risk of outcomes such as spontaneous abortion.[7] This limitation may fuel the misconception that adverse pregnancy outcomes are only associated with heavy consumption and that modest, occasional use is harmless.[8,9]

Spontaneous abortion occurs in an estimated 1 in 6 recognized pregnancies[10,11] and can come at a great emotional cost.[12] Alcohol use may increase the risk of spontaneous abortion through several potential mechanisms: oxidative stress secondary to alcohol consumption may disrupt biochemical pathways involved in embryogenesis; exposure can hinder retinoic acid synthesis, thereby affecting epigenetic programming and cell lineage determination; and alcohol use can alter maternal hormone levels, affecting uterine receptivity.[13] Studies of alcohol use and spontaneous abortion are often hindered by methodologic shortcomings such as recall bias and imprecision in determining gestational age at pregnancy loss.[14] Many recruit participants during prenatal care, meaning enrollment takes place later in gestation than many spontaneous abortions occur. Others are vulnerable to selection bias because of recruitment methods that differ by pregnancy outcome. Prior studies routinely treat alcohol use as an unchanging exposure, which does not reflect the pattern of use for most women.[2,5,6] These factors leave women and care providers with limited access to data about how the timing of alcohol use in pregnancy relates to spontaneous abortion.

In this prospective cohort, we had the opportunity to recruit participants representative of the general obstetrical population. They were enrolled while planning a pregnancy or in early pregnancy and reported alcohol use both before and after any change in drinking. Our primary objective was to incorporate information about week-by-week alcohol use in measures of spontaneous abortion risk.

Materials and Methods

Study population

With institutional review board approval, we recruited women early in pregnancy or planning a pregnancy into

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AJOG at a Glance

Why was this study conducted?

Alcohol use is common in the first weeks of gestation before pregnancy detection. Alcohol is routinely treated as an unchanging exposure, making information about how timing and duration of use relates to spontaneous abortion risk scarce.

Key findings

Each additional week of alcohol exposure during the first trimester increases the risk of spontaneous abortion, even at low levels of consumption and when excluding binge drinking. Alcohol use in weeks 5 through 10 of pregnancy is associated with an increased risk of spontaneous abortion.

What does this add to what is known?

The timing of alcohol use matters, and each additional week of even modest consumption is associated with an increased risk of spontaneous abortion. An emphasis on early detection of pregnancy and cessation of alcohol use could curtail spontaneous abortions linked with exposure.

Right from the Start (RFTS), a prospective cohort. Women were enrolled between 2000 and 2012 from 8 metropolitan areas in North Carolina, Tennessee, and Texas.[15] Recruitment materials were distributed through businesses, community groups, public advertising, direct mail, and prenatal care providers. Eligibility required participants to be aged 18 years or older, English- or Spanish-speaking, no use of fertility treatments, and intention to carry pregnancy to term. Participants were enrolled before 12 completed weeks of gestation (median gestational age at enrollment, 47 days; interquartile range [IQR], 38−58; n=5353) and gave informed consent. Women intending to become pregnant were provided free pregnancy tests for up to 6 months and enrolled at first positive pregnancy test.

Participants completed an intake interview at baseline and a computer-assisted telephone interview during the first trimester. Interviews collected information about demographics, medical history, reproductive history, lifestyle, and health behaviors. Participants had a transvaginal research ultrasound in the first trimester. The median gestational age of ultrasound was 58 days (IQR, 49−69 days).

Exposure

During the first trimester interview, participants provided detailed information about alcohol consumed in the past 4 months (Appendix). This window was selected to capture alcohol exposure immediately before pregnancy and through the first trimester. Participants reported whether they altered alcohol use during this period; date of change in use; frequency, amount, and type of alcohol consumed before and after change; and number of binge episodes, defined as consumption of more than 4 drinks in an episode. Gestational age at change was determined using self-reported last menstrual period (LMP), which is a validated and reliable dating method in this cohort.[16] We used self-reported LMP for gestational dating for all study participants because ultrasound-based dating often underestimates gestational age in pregnancies that go on to end in loss. Number of drinks per week was calculated for before and after change and was evaluated as both a continuous and categorical measure (unexposed, ≤1 drink/week, 1.01−2 drinks/week, 2.01−4 drinks/week, and >4 drinks/week). Beverage type was categorized as wine, beer, or liquor (consumed alone or in mixed drinks).

Outcome

Participants provided pregnancy status at 20 to 25 weeks from LMP. Self-reported pregnancy outcome was corroborated by information abstracted by trained study personnel from vital records, birth certificates, and medical records. Spontaneous abortion was defined as loss of pregnancy before 20 completed weeks of gestation. Pregnancies ending in spontaneous abortion were compared with those surviving past 20 weeks of gestation (live births and stillbirths), and participants with an unknown pregnancy outcome were censored at the date of last study contact. We defined timing of pregnancy outcome among women with spontaneous abortion using 2 approaches: gestational age at spontaneous abortion and gestational age at arrest of development estimated using features observed on research ultrasound before loss.[14] Gestational age at arrest of development was estimated using features observed on research ultrasound before loss, which was not available for 28.6% of participants who had a pregnancy that ended in spontaneous abortion (185/645). Because the distribution of gestational age at arrest differs by gestational age at spontaneous abortion, we assigned gestational age at arrest of development for women without a research ultrasound through random sampling of observed values of gestational age at arrest among women who had a spontaneous abortion in the same gestational week.

Statistical analysis

We used 2 main modeling approaches to quantify risk associated with alcohol use in pregnancy because the timing of alcohol exposure may influence risk in multiple ways. First, we considered alcohol exposure by gestational week of exposure. Second, we evaluated how duration of alcohol exposure relates to risk.

Gestational age−specific exposure

Timing of exposure during pregnancy maps to embryologic development and thus informs risk, so we examined gestational week−specific effects of alcohol use. We performed separate logistic regressions to estimate adjusted odds ratios (aORs) for spontaneous abortion and alcohol exposure (yes/no)

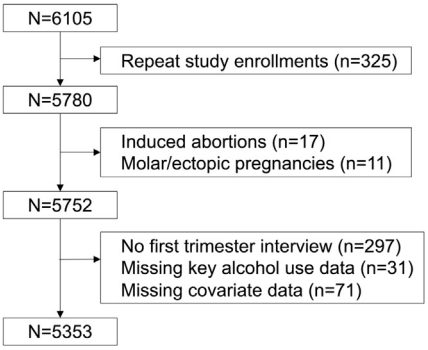
in each gestational week of the first trimester. Participants who did not use alcohol during pregnancy were counted as unexposed for all weeks, and participants who did not change consumption or who only altered amount were considered exposed for all weeks. Participants who stopped using alcohol during the first trimester were classified as exposed in weeks before reported change and unexposed thereafter. Participants were included in week-specific models if they had not yet had a loss or been censored by the beginning of the week.

To evaluate the role of the amount of alcohol consumed, we quantified the association between spontaneous abortion risk and the number of drinks per week in 4 developmental windows in which teratogens are expected to confer risk through different mechanisms: periimplantation (gestational weeks 1−4), early embryonic (gestational weeks 5−7), late embryonic (gestational weeks 8−10), and fetal (gestational weeks 11 and 12).[17] We performed separate logistic regressions for amount of alcohol consumed and spontaneous abortion risk for each window. Logistic regression model fit was assessed using Pearson goodness-of-fit test and Hosmer-Lemeshow test.

Duration of exposure

We also considered that duration of alcohol use during pregnancy may drive risk. We used extended Cox survival models to measure the association between spontaneous abortion and duration of alcohol use, operationalized as the number of days between LMP and time *t* or gestational age at cessation of alcohol use, whichever came first. If a participant reported continuing alcohol use, duration of exposure accumulated until the first trimester interview. We present adjusted hazard ratios (aHRs) associated with each additional week of use. Participants contributed time in the model from day of enrollment through 20 weeks' gestation, arrest of development, or loss to follow-up, whichever came first. Left truncation based on gestational age at enrollment allowed us to more precisely estimate spontaneous abortion risk by taking into account whether a subject had an ongoing pregnancy at cohort entry.[18] Information about the duration of exposure was updated in the model for each gestational day. Once a participant entered the cohort, the cumulative number of days exposed during pregnancy was reflected in the model, thus incorporating information about exposure that occurred before cohort entry while protecting for immortal time bias by not counting events that could not be observed. Given the varying amount of congeners,[19] such as acetaldehyde, in different alcohols, we also evaluated the risk associated with each additional week of exposure by beverage type in a secondary analysis.

FIGURE 1
Flow diagram for study population derivation



Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

Commonalities between approaches

Adjusted models included covariates selected a priori based on a directed acyclic graph of known or suspected relationships with alcohol consumption and spontaneous abortion risk[20]: maternal age (years, spline), race/ethnicity (non-Hispanic white, non-Hispanic black, or other), education (high school or less, some college, and college or more), cigarette use (never smoker or distant quit [more than 4 months before first trimester interview], recent quit, or current smoker), pregnancy intention (intended or unintended),[21] and parity (nulliparous, 1 prior birth, and 2 or more prior births).

We enrolled 6105 women; data from 5353 women were eligible for analysis (Figure 1). Participants who were excluded because they were missing data for 1 or more variables in the covariate set were younger and more likely to be black and have an unintended pregnancy than participants with complete data (n=71; Supplemental Table 1).

We performed a series of sensitivity analyses to determine robustness of results; analyses were repeated with pregnancy endpoint for losses defined as gestational age at spontaneous abortion as opposed to gestational age at arrest of development, with participants without a research ultrasound excluded, and with women who reported binge drinking excluded. We tested for effect modification by maternal body mass index (continuous) and smoking status using the likelihood ratio test for the inclusion of interaction terms. In a secondary analysis, we used Cox proportional hazard models to measure the association between the number of binge episodes (none, 1−3, and ≥4) and spontaneous abortion.

We used 2-sided tests with a significance level of .05. Threshold for significance was Bonferroni-corrected by a factor equal to the number of tests performed in the hypothesis. Analyses were performed in Stata (Version 14.2, StataCorp, College Station, TX).

TABLE 1
Participant characteristics by alcohol use during pregnancy

Characteristic	No alcohol use (n=2691)	Alcohol use[a] (n=2662)	Unadjusted OR	95% CI
Maternal age, n (%), y				
<25	623 (23.2)	418 (15.7)	1.00	Referent
25–29	962 (35.7)	880 (33.1)	1.36	1.17–1.59
30–34	784 (29.1)	936 (35.2)	1.78	1.52–2.08
≥35	322 (12.0)	428 (16.1)	1.98	1.64–2.40
Race/ethnicity, n (%)				
White, non-Hispanic	1723 (64.0)	2052 (77.1)	1.00	Referent
Black, non-Hispanic	634 (23.6)	353 (13.3)	0.47	0.40–0.54
Other	334 (12.4)	257 (9.7)	0.65	0.54–0.77
Education, n (%)				
High school or less	586 (21.8)	340 (12.8)	1.00	Referent
Some college	520 (19.3)	442 (16.6)	1.47	1.22–1.76
College or more	1585 (58.9)	1880 (70.6)	2.04	1.76–2.37
Household income, n (%)				
≤$40,000	967 (35.9)	638 (24.0)	1.00	Referent
$40,001–$80,000	972 (36.1)	967 (36.3)	1.51	1.32–1.72
>$80,000	647 (24.0)	986 (37.0)	2.31	2.01–2.66
Missing	105 (3.9)	71 (2.7)	—	—
Marital status, n (%)				
Married or cohabitating	2395 (88.4)	2401 (90.2)	1.00	Referent
Other	296 (11.6)	261 (9.8)	0.88	0.74–1.05
Parity, n (%)				
Nulliparous	1149 (42.7)	1414 (53.1)	1.00	Referent
1 prior delivery	984 (36.6)	869 (32.6)	0.72	0.64–0.81
2+ prior deliveries	558 (20.7)	379 (14.2)	0.55	0.47–0.64
Prior spontaneous abortion, n (%)				
0	2020 (75.1)	2115 (79.5)	1.00	Referent
1	518 (19.2)	443 (16.6)	0.82	0.71–0.94
≥2	153 (5.7)	104 (3.9)	0.65	0.50–0.84
BMI, n (%), kg/m^2				
<18.5	67 (2.5)	66 (2.5)	0.87	0.62–1.24
18.5–24.9	1334 (49.6)	1505 (56.5)	1.00	Referent
25–29.9	645 (24.0)	610 (22.9)	0.84	0.73–0.96
≥30	607 (22.6)	460 (17.3)	0.67	0.87–0.77
Missing	38 (1.4)	21 (0.8)	—	—
Smoking status,[b] n (%)				
Never or distant quit	2454 (91.2)	2266 (85.1)	1.00	Referent
Current or recent quit	237 (8.8)	396 (14.9)	1.81	1.53–2.15

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021. *(continued)*

TABLE 1
Participant characteristics by alcohol use during pregnancy *(continued)*

Characteristic	No alcohol use (n=2691)	Alcohol use[a] (n=2662)	Unadjusted OR	95% CI
Pregnancy intention, n (%)				
Intended	1983 (73.7)	1940 (72.9)	1.00	Referent
Not intended	708 (26.3)	722 (27.1)	1.04	0.92–1.18
Prenatal vitamin use,[c] n (%)				
No	109 (4.1)	64 (2.4)	1.00	Referent
Yes	2582 (95.9)	2598 (97.6)	1.71	1.25–2.34
Illicit drug use,[c] n (%)				
No	2599 (96.6)	2400 (90.2)	1.00	Referent
Yes	92 (3.4)	262 (9.8)	3.08	2.42–3.94
Intimate partner violence,[c] n (%)				
No	2624 (97.5)	2579 (96.9)	1.00	Referent
Yes	62 (2.3)	79 (3.0)	1.30	0.93–1.82
Missing	5 (0.2)	4 (0.15)	—	—

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

[a] Alcohol use defined as exposure past last menstrual period; [b] Quitting within the 4 months before the end of first trimester interview is considered a recent quit, and quitting before that time is considered a distant quit; [c] Any history during the 4 months before the first trimester interview.

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

Results

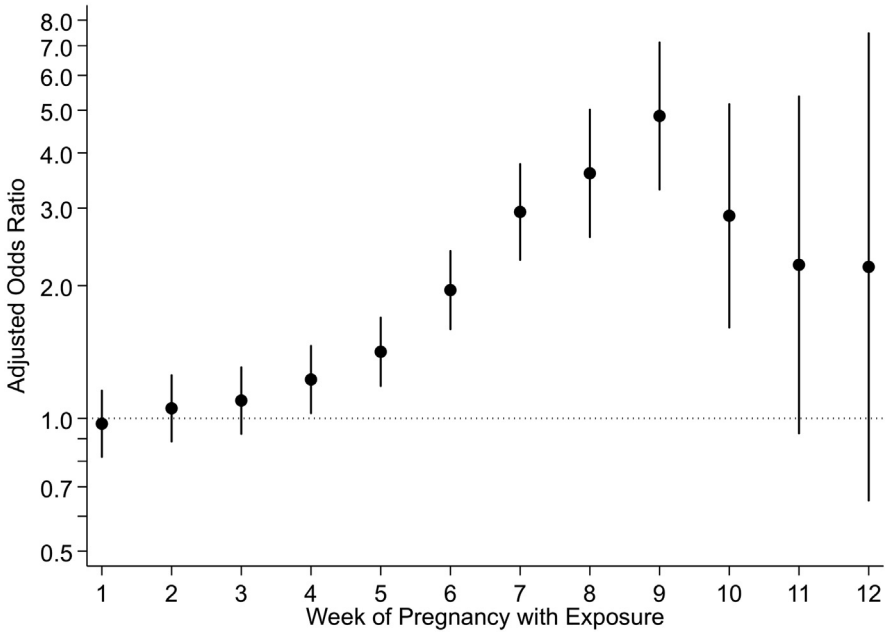
Among 5353 women, 14.1% reported never using alcohol, 36.2% quit before LMP, 44.3% quit after LMP, and 5.4% continued use. Among 2926 women who reported a change in alcohol exposure within the month before conception or during the first trimester, 91.5% quit using alcohol, 8.0% decreased use, and 0.5% increased use. Median gestational age at change was 29 days (IQR, 15–35 days) and 41.0% of participants who reported a change altered use within 3 days of a positive pregnancy test (1214/2962). Higher maternal age, household income, level of education, prenatal vitamin use, and illicit drug use were associated with alcohol exposure during pregnancy (Table 1). Non-Hispanic white women, nulliparous women, and smokers were more likely to be exposed to alcohol during pregnancy than their counterparts. Participants who were exposed to alcohol consumed a median of 2 drinks per week at the onset of pregnancy (IQR, 1–4 drinks per week). At least 1 binge episode during the periconception period or first trimester was reported by 11.0% of women (591/5349). The median number of binge episodes was 2 (IQR, 1–4), and 10.3% of participants who binged reported 10 or more episodes (61/591).

Furthermore, 12% of pregnancies ended in spontaneous abortion (645/5353). When considering week-specific exposure, alcohol use in gestational weeks 5 through 10 was associated with spontaneous abortion after adjusting for multiple comparisons (aOR range, 1.42–4.85; Figure 2; Supplemental Table 2). Risk peaked for exposure in week 9 of gestation (aOR, 4.85; 95% confidence interval [CI], 3.30–7.13). These results were consistent between the 2 approaches used for defining timing of outcome (Supplemental Figure) and when excluding participants who reported binge drinking. A dose-response trend was not detected in any developmental window (Supplemental Table 3).

Each additional week of alcohol exposure during pregnancy was associated with an 8% relative increase in the risk of spontaneous abortion compared with the risk among women who were unexposed (aHR, 1.08; 95% CI, 1.04–1.12; Table 2). Participants who were exposed to alcohol up until 29 days of gestation (the median gestational age of alcohol use cessation in the cohort) had a 37% greater risk of spontaneous abortion relative to participants who were unexposed (aHR, 1.37; 95% CI, 1.18–1.60). Alcohol use in the lowest exposure category (≤1 drink per week) was associated with elevated risk in a way that was not different than estimates for higher levels of exposure (Table 2). Estimates did not vary by alcohol type (P=.99, Wald test) or when excluding participants who reported binge drinking. In addition, estimates did not differ when excluding pregnancies ending in a spontaneous abortion without a research ultrasound (Supplemental Table 4) or when defining pregnancy endpoint as the gestational age at spontaneous abortion (Supplemental Table 5).

We did not observe modification of the association between alcohol use and spontaneous abortion by maternal body mass index or smoking status. The number of binge episodes was not associated with spontaneous abortion risk (0 episodes [referent]; 1–3 episodes: aHR, 0.75; 95% CI, 0.48–1.15; ≥4 episodes: aHR, 0.88; 95% CI, 0.43–1.80), and inclusion of binge

FIGURE 2
Risk of spontaneous abortion by gestational week with alcohol exposure (n = 5353)



Pregnancy endpoint defined as the gestational age at arrest of development. Estimates adjusted for maternal age, race/ethnicity, education, parity, smoking status, and pregnancy intention. Weeks 5 through 10 are significant after adjusting for multiple comparisons (Bonferroni-corrected with a factor of 12).

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

drinking in the main models did not alter findings. Any illicit drug use within 4 months leading up to the first trimester was reported by 6.6% of participants. Of the participants who reported illicit drug use, 84.2% reported marijuana as the only exposure (298/354). Intimate partner violence within the 4 months before the first trimester interview was reported by 2.6% of participants, and physical harm was reported by 1.3% of participants (n=9 did not respond). Including illicit drug use and intimate partner violence as covariates in the adjusted estimates did not alter results.

Comment

Principal findings

In this prospective, community-recruited cohort, the timing of alcohol use is a key determinant of spontaneous abortion. Alcohol exposure occurred in half of the pregnancies, with many participants not changing use until a positive pregnancy test. Each additional week of alcohol use in the first trimester was associated with a cumulative increase in the risk of spontaneous abortion, and risk was most strongly related to exposure in weeks 5 through 10 of pregnancy. This window aligns with the embryonic stage of development, when organogenesis is occurring and pregnancy is most vulnerable to insults.[22,23] These findings persisted when excluding women who reported binge drinking.

Women who were older than 35 years, white, college-educated, and from high-income households were most likely to use alcohol. Although this is not the population generally flagged for high-risk behaviors, these demographics are consistently linked with alcohol use during pregnancy.[3,5,24,25] Clinical biases may result in these women being overlooked for risk counseling even though this group is at the greatest risk for modest, continued alcohol use.

Results in context

Prior studies of alcohol exposure and spontaneous abortion risk are limited by the methods used for ascertaining and modeling exposure.[7] Many define exposure as alcohol use after pregnancy recognition. In RFTS, this definition misclassifies 44.3% of participants as unexposed. Others calculate an across-pregnancy average dose or describe prepregnancy alcohol use and its associated risk separately. An across-pregnancy average dose neglects that exposure is likely concentrated in early pregnancy. Evaluating prepregnancy exposure separately without considering how long use persists disregards that risk may be tied to gestational age at exposure. Alcohol use typically occurs before pregnancy detection and rapidly tapers thereafter. Therefore, most exposure co-occurs with the first stages of embryo development. Our results suggest that the timing of exposure is critical in understanding spontaneous abortion risk.

Strengths and limitations

Before considering the implications of these findings, let us audit the level of confidence we should have in the results. We relied on self-report to determine alcohol use because no sufficiently sensitive and specific biomarker for alcohol exposure exists.[26] Social desirability bias, or responding in a way deemed favorable by others, may lead women to underreport alcohol use during pregnancy.[27,28] We attempted to minimize this bias by conducting telephone interviews in a nonclinical and confidential setting using questionnaires with nonjudgmental wording and unknown interviewers. Prevalence of alcohol use at the onset of pregnancy in this cohort aligns with national data about exposure among nonpregnant, reproductive-aged women,[5,29] which provides reassurance that social desirability bias did not unduly suppress reporting about the presence of alcohol exposure.

Assessment of alcohol exposure followed loss for 67.2% of spontaneous abortions (436/649), allowing potential for recall bias.[30] However, the proportion of women with losses who reported

TABLE 2
Risk of spontaneous abortion associated with each additional week of alcohol use during pregnancy

Alcohol use[a] characteristic	Births (n=4708) n (%)	Spontaneous abortions (n=645) n (%)	Crude HR	95% CI	Adjusted HR[b]	95% CI
			Per additional week		Per additional week	
Any use						
No	2367 (50.3)	324 (50.2)	1.00	Referent	1.00	Referent
Yes[c]	2341 (49.7)	321 (49.8)	1.09	1.05–1.13	1.08	1.04–1.12
Amount at LMP[d]						
Unexposed	2367 (50.3)	324 (50.2)	1.00	Referent	1.00	Referent
≤1 drink/wk[c]	931 (19.8)	120 (18.6)	1.09	1.05–1.14	1.08	1.04–1.13
1.01–2 drinks/wk	449 (9.5)	67 (10.4)	1.06	1.00–1.12	1.06	1.00–1.12
2.01–4 drinks/wk	440 (9.3)	60 (9.3)	1.05	1.00–1.10	1.05	1.00–1.10
>4 drinks/wk	521 (11.1)	74 (11.5)	1.02	0.97–1.07	1.00	0.96–1.05
Alcohol type[e]						
Wine[c]	1545 (32.8)	201 (31.2)	1.07	1.03–1.11	1.07	1.02–1.11
Beer[c]	1089 (23.1)	138 (21.4)	1.07	1.02–1.12	1.07	1.02–1.12
Liquor	858 (18.2)	106 (16.4)	1.03	0.97–1.09	1.04	0.98–1.10

CI, confidence interval; *HR*, hazard ratio; *LMP*, last menstrual period.

[a] Alcohol modeled as a time-varying exposure for duration of use, left truncation based on gestational age at enrollment; [b] Adjusted for maternal age (continuous, spline), race/ethnicity, education, parity, smoking status, and pregnancy intention; [c] Significant after adjustment for multiple comparisons (Bonferroni-corrected with a factor of 4 for amount consumed and 3 for alcohol type); [d] Categories reflect level of alcohol consumption before change in use, duration defined as prechange use; [e] Alcohol type categories do not total 100% because they are not mutually exclusive. Women who reported alcohol exposure in pregnancy but did not provide alcohol type are excluded from this analysis (n=30). Referent group is women unexposed to alcohol.

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

alcohol exposure during pregnancy did not differ by interview timing before or after loss (chi-square *P* value=.78), and gestational age at change in alcohol consumption was similar between the groups (median 31 days vs 32 days; Wilcoxon rank-sum *P* value=.36).

We did not observe a dose-response relationship between alcohol exposure and risk. Although many biological relationships operate on a dose-dependent gradient, the timing of alcohol use may drive spontaneous abortion risk with a threshold effect observed at low levels of exposure. In fetal alcohol spectrum disorder, a dose-response relationship is not always the rule.[31,32] Facial abnormalities characteristic of fetal alcohol spectrum disorder can be observed for low levels of alcohol use if exposure occurs when neural crest cells are migrating to form facial structures,[33] and changes in neonatal brain activity are observed with low levels of prenatal alcohol exposure.[34] Alternatively, imprecision or bias in reporting the amount of alcohol consumed may obscure a dose-dependent effect. Because alcohol use during pregnancy is stigmatized, information about the amount consumed may be more vulnerable to reporting biases than responses about mere presence or absence of exposure. In addition, misconceptions about size and alcohol content of a standard drink may lead to error in earnest reporting.

RFTS prioritized early recruitment of pregnancies to capture as many spontaneous abortion events as possible; 25.8% of participants entered the study before conceiving and 71.6% enrolled before 7 weeks' gestation. The proportion of participants who were exposed to alcohol in early pregnancy and timing of change in alcohol use was similar when comparing women who enrolled before conception with those who enrolled in the first trimester, and results are unchanged when excluding participants who were enrolled before conception. Recruitment before conception or initiation of prenatal care enabled earlier enrollment than clinic-based studies. Although this is an improvement over many studies of spontaneous abortion, losses occurring very early in gestation are inevitably underrepresented in this sample. We truncated time before enrollment in survival analyses to account for a participant having an ongoing pregnancy at study entry. Risk associated with alcohol use in the first weeks of pregnancy may be higher than estimated if unobserved early losses were highly associated with alcohol exposure.

Because this cohort required early enrollment, this study also has a higher proportion of planned pregnancies than the general population (73% vs 51%).[21] The proportion of participants exposed to alcohol at pregnancy onset and timing of change in drinking was similar for participants with intended and unintended pregnancies, indicating planned pregnancies do not necessarily involve preparatory changes in alcohol use. Of women who were exposed, 40%

reported quitting alcohol use within 3 days of a positive pregnancy test.

Less than 1% of participants reported a history of type 1 or type 2 diabetes, and results were unchanged when diabetes was included in the adjusted model. A priori, we determined there would be insufficient power to address other medical conditions associated with early pregnancy loss, such as infection or maternal antiphospholipid syndrome. These conditions are rare and unlikely to influence findings of a large cohort. When limiting the analysis to women who had at least 1 prior live birth, and therefore proven capacity for a successful pregnancy, results were unchanged.

Conclusions and implications

Studies not accounting for alcohol exposure in early pregnancy obscure the time-dependent effect of alcohol use and underestimate risk. In this prospective cohort, we find that risk of spontaneous abortion accumulates with each successive week of alcohol use, even at low levels of consumption and when excluding binge drinking. These findings underscore the warning of no known safe amount of alcohol in pregnancy.[35] Optimally, exposure would be completely prevented; still, half of pregnancies in the United States are unintended and abstaining from alcohol when planning a pregnancy is not typical. Because home pregnancy testing reliably detects pregnancy as early as 4 weeks' gestation and alcohol use in weeks 5 through 10 is most concerning for risk, there is a window of opportunity. Therefore, efforts to promote early pregnancy recognition and cessation of alcohol use are warranted to curtail risk of spontaneous abortion. ■

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Appendix

Questionnaire items about alcohol consumption in first trimester interview.

- Have you ever had alcoholic beverages, like beer, wine, or liquor including gin, whiskey, rum, or mixed drinks?
- At this time, do you drink any alcoholic beverages, like beer, wine, or liquor including gin, whiskey, rum, or mixed drinks?
- How often do you drink an alcoholic beverage, by that I mean at least one beer, one glass of wine, one mixed drink, or one shot of liquor? *(# times per day, week, or month, or less than once per month).*
- On those occasions that you drink alcoholic beverages, how many drinks do you usually have?
- At this time, what type(s) of alcohol do you usually drink? To make it easier for you to respond, I'm going to read you a list of options: beer, wine, mixed drinks, shot of liquor, other alcohol _____.
- Did you stop drinking alcoholic beverages in the past 4 months or more than 4 months ago?
- In the past 4 months, have you changed how often and/or how many alcoholic beverages you drink?
- When did this change occur?
- Do you remember what week in [month] that was, the first, second, third, fourth, or fifth?
- Before this change, how often did you drink? *(# times per day, week, or month, or less than once per month).*
- Before this change, on those occasions when you drank alcoholic beverages, how many drinks did you usually have on each occasion?
- What type(s) of alcohol did you usually drink? Did you drink beer, wine, mixed drinks, shot of liquor, other alcohol _____.
- In the past four months, have you had more than four drinks on any one occasion?
- How many times in the past four months have you had more than four drinks on any occasion?
- On those occasions when you had more than four drinks, what type(s) of alcohol did you usually drink? Did you drink beer, wine, mixed drinks, shot of liquor, other alcohol _____.

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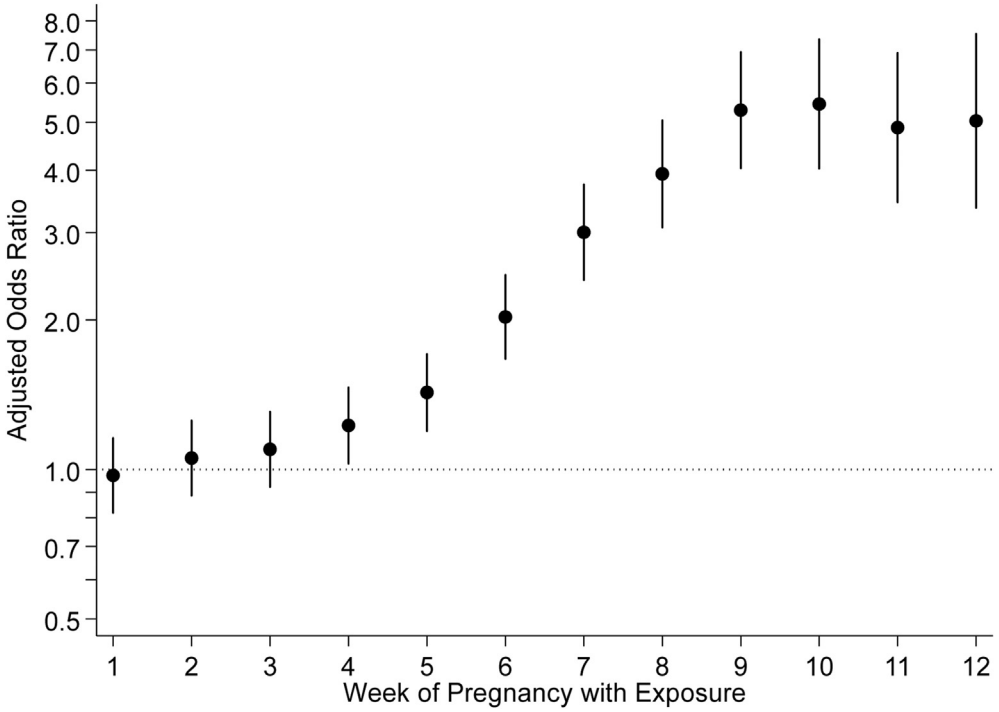
SUPPLEMENTAL FIGURE

Risk of spontaneous abortion by gestational week with alcohol exposure; pregnancy endpoint defined as gestational age at spontaneous abortion



Estimates are adjusted for maternal age, race/ethnicity, education, parity, smoking status, and pregnancy intention. Participants with complete data for adjusted analysis are included (n=5353). Weeks 5 through 12 are significant after adjusting for multiple comparisons (Bonferroni-corrected with a factor of 12). Black dot represents adjusted odds ratio, black line spans 95% confidence interval, and dotted line indicates an odds ratio of 1.

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 1

Comparison of participants with complete covariate data with those missing data for 1 or more covariates

Characteristic	Complete case (n=5353)	Missing covariates (n=71)	*P* value[a]
Maternal age, median (IQR), y	29 (26–32)	25 (21–30)	<.01
Race/ethnicity, n (%)			<.01
White, non-Hispanic	3775 (70.5)	16 (22.5)	
Black, non-Hispanic	987 (18.4)	39 (54.9)	
Other	591 (11.0)	13 (18.3)	
Refused	0 (0.0)	3 (4.2)	
Education, n (%)			<.01
High school or less	926 (17.3)	42 (59.2)	
Some college	962 (18.0)	14 (19.7)	
College or more	3465 (64.7)	14 (19.7)	
Missing	0 (0.0)	1 (1.4)	
Marital status, n (%)			<.01
Married or cohabitating	4796 (89.6)	43 (60.6)	
Other	557 (10.4)	28 (39.4)	
Parity, n (%)			.01
Nulliparous	2563 (47.9)	6 (8.5)	
1 prior delivery	1853 (34.6)	2 (2.8)	
2+ prior deliveries	937 (17.5)	5 (7.0)	
Missing	0 (0.0)	58 (81.7)	
Smoking status, n (%)[b]			<.01
Never or distant quit	4720 (88.2)	53 (74.6)	
Current or recent quit	633 (11.8)	18 (25.4)	
Pregnancy intention, n (%)			<.01
Intended	3923 (73.3)	23 (32.4)	
Not intended	1430 (26.7)	37 (52.1)	
Missing	0 (0.0)	11 (15.5)	
Alcohol use, n (%)[c]			.23
Yes	2662 (49.7)	30 (42.3)	
No	2691 (50.3)	41 (57.7)	
Gestational age at change, median (IQR), d	29 (15–35)	22 (6–35)	.10
Consumption at LMP, median (IQR), drinks/wk	2.0 (1.0–4.0)	2.0 (0.3–3.0)	.27
Pregnancy outcome, n (%)			.14
Spontaneous abortion	645 (12.0)	4 (5.6)	
No spontaneous abortion	4708 (88.0)	67 (93.4)	

IQR, interquartile range; *LMP*, last menstrual period.

[a] *P* value calculated using Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables (missing not included); [b] Quitting within the 4 months before the end of first trimester interview is considered a recent quit and quitting before that time is considered a distant quit; [c] Alcohol use is defined as use past LMP.

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 2

Risk of spontaneous abortion by gestational week of alcohol exposure

Week of alcohol exposure	Births[a]	Spontaneous abortion[a]	Adjusted OR[b]	95% CI
Gestational wk 1	4708	645	0.97	0.81–1.16
Gestational wk 2	4708	645	1.05	0.89–1.25
Gestational wk 3	4708	645	1.10	0.92–1.31
Gestational wk 4	4708	645	1.23	1.03–1.46
Gestational wk 5[c]	4708	642	1.42	1.18–1.69
Gestational wk 6[c]	4708	574	1.95	1.59–2.40
Gestational wk 7[c]	4708	446	2.94	2.29–3.77
Gestational wk 8[c]	4708	279	3.60	2.58–5.02
Gestational wk 9[c]	4705	215	4.85	3.30–7.13
Gestational wk 10[c]	4705	136	2.88	1.61–5.16
Gestational wk 11	4702	83	2.23	0.93–5.38
Gestational wk 12	4700	52	2.21	0.65–7.47

CI, confidence interval; *OR*, odds ratio.

[a] Counts reflect participants who contributed to each week-specific model. Participants were only included if they had complete data for adjusted analysis and had not had a spontaneous abortion or been censored by the beginning of the week; [b] Adjusted for maternal age (continuous, spline), race/ethnicity, education, parity, smoking status, and pregnancy intention; [c] Significant after adjustment for multiple comparisons (Bonferroni-corrected with a factor of 12).

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 3

Risk of spontaneous abortion associated with the amount of alcohol consumed in 3 developmental windows

Alcohol use characteristic	Births n[a]	Births %	Spontaneous abortions n[b]	Spontaneous abortions %	Crude OR	95% CI	Adjusted OR[c]	95% CI
Weeks 1–4	4708		645					
Unexposed	2367	50.3	324	50.2	1.00	Referent	1.00	Referent
≤1 drink/wk	931	19.8	120	18.6	0.94	0.75–1.18	0.91	0.73–1.14
1.01–2 drinks/wk	449	9.5	67	10.4	1.09	0.82–1.44	1.11	0.83–1.48
2.01–4 drinks/wk	440	9.3	60	9.3	1.00	0.74–1.34	0.98	0.72–1.33
>4 drinks/wk	521	11.1	74	11.5	1.04	0.79–1.36	0.97	0.73–1.29
Weeks 5–7	4708		642					
Unexposed	3240	68.8	393	61.2	1.00	Referent	1.00	Referent
≤1 drink/wk[d]	537	11.4	96	15.0	1.47	1.16–1.88	1.44	1.12–1.84
1.01–2 drinks/wk	279	5.9	49	7.6	1.45	1.05–1.99	1.52	1.09–2.11
2.01–4 drinks/wk	282	6.0	45	7.0	1.32	0.94–1.83	1.38	0.98–1.94
>4 drinks/wk	370	7.9	59	9.2	1.31	0.98–1.76	1.32	0.97–1.80
Weeks 8–10	4708		379					
Unexposed	4434	94.2	223	79.9	1.00	Referent	1.00	Referent
≤1 drink/wk[d]	181	3.8	41	14.7	4.50	3.13–6.49	3.97	2.71–5.83
1.01–2 drinks/wk	37	0.8	6	2.2	3.22	1.35–7.72	2.98	1.21–7.37
2.01–4 drinks/wk	32	0.7	4	1.4	2.49	0.87–7.09	2.29	0.79–6.64
>4 drinks/wk	24	0.5	5	1.8	4.14	1.57–10.96	3.42	1.25–9.35

CI, confidence interval; *OR*, odds ratio.

[a] We were not able to estimate dose-specific effects for exposure in the fetal window because alcohol exposure was rare late in the first trimester; [b] Counts reflect participants that contributed to analysis for each developmental window. Participants were included if they had complete data for adjusted analysis and had not had a spontaneous abortion or been censored by the beginning of the week; [c] Adjusted for maternal age (continuous, spline), race/ethnicity, education, parity, smoking status, and pregnancy intention; [d] Significant after adjustment for multiple comparisons (Bonferroni-corrected with a factor of 12).

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 4

Risk of spontaneous abortion associated with each additional week of alcohol use during pregnancy, cases restricted to those with ultrasound data

Alcohol use[a] characteristic	Births (n=4708)[b]		Spontaneous abortions (n=462)[b]		Crude HR	95% CI	Adjusted HR[c]	95% CI
	n	%	n	%	Per additional week		Per additional week	
Any use								
No	2367	50.3	239	51.7	1.00	Referent	1.00	Referent
Yes[d]	2341	49.7	223	48.3	1.08	1.04–1.13	1.07	1.03–1.12
Amount at LMP[e]								
Unexposed	2367	50.3	239	51.7	1.00	Referent	1.00	Referent
≤1 drink/wk[d]	931	19.8	74	16.0	1.07	1.02–1.13	1.06	1.01–1.12
1.01–2 drinks/wk	449	9.5	49	10.6	1.07	1.00–1.13	1.07	1.00–1.13
2.01–4 drinks/wk	440	9.3	45	9.7	1.05	0.99–1.11	1.05	0.99–1.11
>4 drinks/wk	521	11.1	55	11.9	1.03	0.98–1.09	1.01	0.96–1.07
Alcohol type[f]								
Wine[d]	1545	32.8	138	29.9	1.07	1.02–1.12	1.06	1.01–1.11
Beer[d]	1089	23.1	96	20.8	1.07	1.02–1.13	1.07	1.01–1.12
Liquor	858	18.2	79	17.1	1.03	0.96–1.10	1.03	0.96–1.10

CI, confidence interval; *HR*, hazard ratio; *LMP*, last menstrual period.

[a] Alcohol modeled as a time-varying exposure for duration of use, left truncation based on gestational age at enrollment; [b] Participants with research ultrasound for estimation of gestational age at arrest of development are included in this table (n=5170); [c] Adjusted for maternal age (continuous, spline), race/ethnicity, education, parity, smoking status, and pregnancy intention; [d] Significant after adjustment for multiple comparisons (Bonferroni-corrected with a factor of 4 for amount consumed and 3 for alcohol type); [e] Categories reflect level of alcohol consumption before change in use, duration defined as prechange use; [f] Alcohol type categories do not total 100% because they are not mutually exclusive. Women who reported alcohol exposure in pregnancy but did not provide alcohol type are excluded from this analysis (n=30). Referent group is women unexposed to alcohol.

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 5

Risk of spontaneous abortion associated with each additional week of alcohol use during pregnancy; pregnancy endpoint defined as gestational age at spontaneous abortion

Alcohol use[a] characteristic	Births (n=4708)		Spontaneous abortions (n=645)		Crude HR	95% CI	Adjusted HR[b]	95% CI
	n	%	n	%	Per additional week		Per additional week	
Any use								
No	2367	50.3	324	50.2	1.00	Referent	1.00	Referent
Yes[c]	2341	49.7	321	49.8	1.10	1.07–1.13	1.09	1.07–1.12
Amount at LMP[d]								
Unexposed	2367	50.3	324	50.2	1.00	Referent	1.00	Referent
≤1 drink/wk[c]	931	19.8	120	18.6	1.09	1.06–1.12	1.07	1.04–1.11
1.01–2 drinks/wk[c]	449	9.5	67	10.4	1.08	1.05–1.12	1.08	1.04–1.12
2.01–4 drinks/wk[c]	440	9.3	60	9.3	1.06	1.02–1.10	1.06	1.02–1.10
>4 drinks/wk	521	11.1	74	11.5	1.04	1.01–1.08	1.03	1.00–1.07
Alcohol type[e]								
Wine[c]	1545	32.8	201	31.2	1.08	1.06–1.11	1.08	1.05–1.11
Beer[c]	1089	23.1	138	21.4	1.09	1.05–1.12	1.09	1.15–1.12
Liquor[c]	858	18.2	106	16.4	1.07	1.03–1.11	1.08	1.04–1.12

CI, confidence interval; *HR*, hazard ratio; *LMP*, last menstrual period.

[a] Alcohol modeled as a time-varying exposure for duration of use, left truncation based on gestational age at enrollment; [b] Adjusted for maternal age (continuous, spline), race/ethnicity, education, parity, smoking status, and pregnancy intention; [c] Significant after adjustment for multiple comparisons (Bonferroni-corrected with a factor of 4 for amount consumed and 3 for alcohol type); [d] Categories reflect level of alcohol consumption before change in use, duration defined as prechange use; [e] Alcohol type categories do not total 100% because they are not mutually exclusive. Women who reported alcohol exposure in pregnancy but did not provide alcohol type are excluded from this analysis (n=30). Referent group is women unexposed to alcohol.

Sundermann et al. Alcohol use and spontaneous abortion. Am J Obstet Gynecol 2021.